TAI® DIAGNOSTICS

Monitoring the Health of Transplanted Organs

INSTRUCTION MANUAL

myTAI HEART

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MKT-015 v2.0

TAI® DIAGNOSTICS

Monitoring the health of transplanted organs

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SECTION I: INTENDED USE

myTAI$_{HEART}$ is a laboratory developed test (LDT) performed in a single laboratory, which measures the donor fraction of cell-free DNA (cfDNA) in plasma separated from a whole blood sample as a marker for transplanted organ injury. This test is intended to aid in the identification of heart transplant recipients who have a low probability of moderate/severe acute cellular rejection (Grade 2R or higher) at the time of testing in conjunction with standard clinical assessment. This test is indicated for use in heart transplant recipients who are 2 months of age or older and ≥ 8 days post-transplant.

SECTION II: WARNINGS AND LIMITATIONS

myTAI$_{HEART}$ quantitates the donor fraction of cfDNA in the circulation of heart transplant recipients. This test may provide a false positive or false negative result under certain clinical conditions. Patients treated for rejection within 28 days before sample collection may have variale donor fractions. Clinical judgment will be required for interpretation of results. A heart transplant recipient with a negative result should continue to be monitored according to standard clinical care. All results should be interpreted in the context of the patient's clinical findings, history, and laboratory results. Clinical correlation is advised.

CONTRAINDICATIONS:

myTAI$_{HEART}$ is currently for use in single organ post-transplant patients. This test is not intended for patients who:

- are pregnant
- have another transplanted organ (solid or allogenic bone marrow)
- have post-transplant lymphoproliferative disease
- currently have cancer, or have had cancer within the previous 2 years
- are on mechanical circulatory support
- are closely related to the donor providing the organ for transplant

Note: If donor is closely related to heart transplant recipient, contact TAI Diagnostics to discuss eligibility for myTAI$_{HEART}$ testing.

This test was developed and its performance characteristics determined by TAI Diagnostics. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. This test is used for clinical purposes. It should not be regarded as investigational or for research. This Laboratory is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high complexity clinical laboratory testing.

SECTION III: INTRODUCTION

Today in the United States, over 180,000 people are living with solid organ transplants. Each year over 2,000 heart transplants, including 300 pediatric heart transplants, are performed resulting in over 20,000 living heart transplant recipients[1]. One year survival following heart transplantation has improved to 90%. However, 10 year survival remains less than 60%[2]. The heart rejection rate for the first year is approximately 15% and in the second year is approximately 5%. Rejection following solid organ transplantation is the major determinant of clinical outcome. Early treatment with immunosuppressive therapy improves graft function and survival, and decreases recipient mortality[3].

TAI Diagnostics provides non-invasive and highly sensitive diagnostic tests to monitor the health of patients who have received solid organ transplants. myTAI$_{HEART}$ is a non-invasive test that requires only a small blood sample for processing in our accredited clinical reference lab and utilizes patent-pending quantitative genotyping technology to measure graft health in heart transplant patients. The technology precisely quantifies the DNA released by injured heart cells into the bloodstream as a direct measurement of transplant injury. TAI Diagnostics' scientific data[4] indicates that the quantitative genotyping technique has a high degree of sensitivity and specificity, and a rapid turnaround time.

SECTION IV: SUMMARY AND EXPLANATION OF THE myTAI$_{HEART}$ TEST

TEST DESCRIPTION

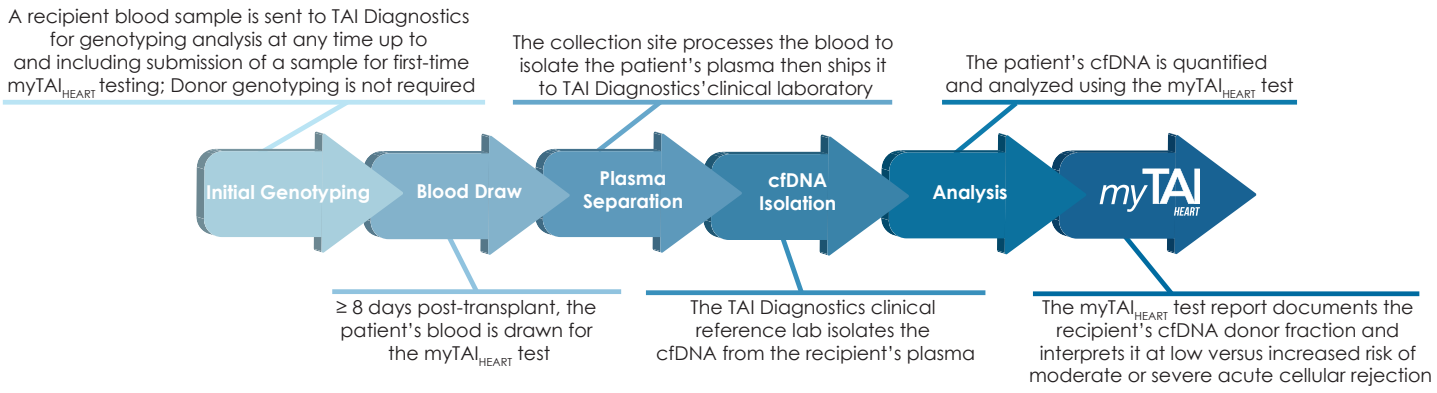
The myTAI$_{HEART}$ test uses a panel of highly informative single nucleotide polymorphisms to quantitatively genotype cell-free DNA (cfDNA) in the patient's plasma. This measurement accurately distinguishes "donor specific" cfDNA originating in the engrafted heart from "self specific" cfDNA originating in the recipient's native cells. The myTAI$_{HEART}$ test reports the ratio of donor specific cfDNA to total cfDNA as the donor fraction (%) and categorizes the patient as at low or increased risk of moderate (grade 2R) to severe (grade 3R) acute cellular rejection. Results and additional data are provided to the ordering clinician on the TAI Diagnostics – myTAI$_{HEART}$ Results Report.

TESTING PROCESS

The testing process for the myTAI$_{HEART}$ is diagrammed in the figure below. Prior to ordering the myTAI$_{HEART}$ test for the first time, initial genotyping analysis must be performed on the patient (heart transplant recipient). Instructions on obtaining and shipping recipient specimens for initial genotyping analysis can be found on our website (www.taidiagnostics.com) or by contacting our Customer Support Department (1-888-214-3151).

At TAI Diagnostics, the patient's cfDNA is isolated, then quantified and processed using the myTAI$_{HEART}$ test. The results are reported to the ordering physician on the next business day (upon receipt at TAI Diagnostics' clinical lab). The physician then interprets the results and determines the course of action for the patient. More details can be found in Section XIII: *Test Requisition Form (TRF) and Test Orders*.

Figure 1: Overview of the myTAI$_{HEART}$ Testing Process



SECTION V: CUSTOMER SUPPORT CONTACT INFORMATION

TAI DIAGNOSTICS CUSTOMER SUPPORT

Telephone	1-888-214-3151
Fax	1-888-300-9674
Email	customersupport@taidiagnostics.com

ORDERING KITS

myTAI$_{HEART}$ kits with prepaid return shipping are available for U.S. clients. To order kits, submit requests through our electronic order form (see website) or contact our customer support department at the telephone number and email address listed below.

Telephone	1-888-214-3151
Email	customersupport@taidiagnostics.com

Business Hours: 8 AM to 5 PM Monday through Friday (Central Standard Time). Contact TAI Diagnostics if shipping samples outside of normal business hours.

SECTION VI: EQUIPMENT AND SUPPLIES REQUIRED BY USER

- Hospital / Laboratory labels containing a minimum of patient name and date of birth (total of 5 needed)
- Parafilm®
- Transfer pipette
- Racks capable of holding 15 mL conical centrifuge tubes
- Variable speed centrifuge capable of spinning at 1100 x g (RCF)
- Swinging bucket rotor(s) that can accommodate 15 mL conical centrifuge tubes and 8.5 mL EDTA Plasma Preparation Tubes (PPT Tubes).
- Freezer (-20˚C or colder)
- Approximately 7 pounds of dry ice per shipment
- Packaging tape

SECTION VII: SUPPLIES PROVIDED BY TAI DIAGNOSTICS

QUANTITY	ITEM
1	Kit Contents Card
1	Insulated Styrofoam shipper with transport box
1	Clear plastic bag
1	Foam tube holder
1	Specimen biohazard bag
2	8.5 mL BD Vacutainer® PPT™ Plasma Preparation Tubes (PPT Tubes)
4	15 mL Eppendorf® Conical Centrifuge Tubes
2	Sterile Transfer Pipettes
1	myTAI$_{HEART}$ Test Requisition Form
1	myTAI$_{HEART}$ Instruction Manual
1	Return overnight shipping label
1	Dry ice shipping label

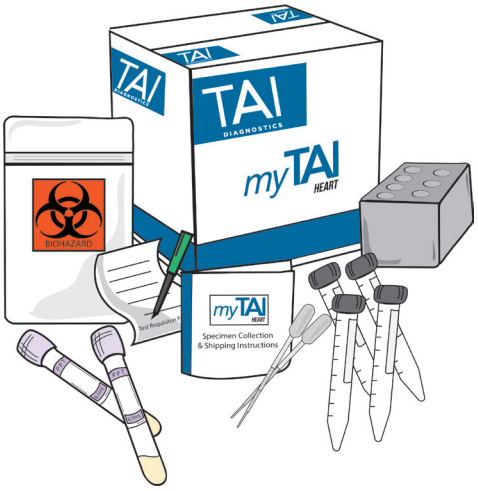


Figure 2: myTAI$_{HEART}$ Testing Kit

STORAGE CONSIDERATIONS

All items provided by TAI Diagnostics in the myTAI$_{HEART}$ testing kit can be stored at room temperature (18 to 25°C). Do not use kits past their indicated expiration date.

SECTION VIII: DISCLAIMERS AND PRECAUTIONS

- This test is for use with whole blood specimens.
- Avoid contamination of specimens and materials used in the myTAI$_{HEART}$ test.
- Take care not to cross-contaminate samples.

- Do not use kits past their expiration date.
- All disposable items are one time use only. Do not reuse.
- When drawing patient blood, follow your laboratory's universal precautions for blood borne pathogens.
- The provided EDTA PPT Tubes are unique to the test and should not be switched with other laboratory tubes.

SECTION IX: ORDER PROCESS

- Wear appropriate personal protective equipment as specified in your laboratory's safety policy.

Additional myTAI$_{HEART}$ Test Requisition Forms (TRFs) can be requested via our website (www.taidiagnostics.com) or by contacting our Customer Support Department. To request pre-printed forms with your laboratory information, please submit a request to our customer support team at customersupport@taidiagnostics.com.

Labeling Tubes: Always affix a hospital / laboratory label that includes at least two patient identifiers to each tube used from the collection kit. Use only the tubes provided by TAI Diagnostics in the collection kit.

Pre-Transplant Appointment

Anytime prior, preferably, days or weeks prior to implant of the heart, blood is collected from the patient into a labeled EDTA plasma preparation tube. This tube should be packaged and shipped according to your laboratory's protocol for whole blood shipment to TAI Diagnostics. TAI Diagnostics will perform initial gentoyping and the results will be utilized for all subsequent post-transplant myTAI$_{HEART}$ testing.

Time of Transplant

If the recipient's whole blood specimen was not obtained for initial genotyping analysis at a previous pre-transplant appointment, a whole blood sample (EDTA purple top) will need to be drawn and sent before or concurrent with submission of the first myTAI$_{HEART}$ specimen.

Post-Transplant Monitoring: myTAI$_{HEART}$ Test (Donor Fraction Analysis)

≥8 days post-transplant, blood is collected from the patient in the provided EDTA PPT Tubes, labeled appropriately. The laboratory processes the blood according to the myTAI$_{HEART}$ procedure and ships the recipient's plasma and the remaining buffy coat and packed red blood cells on dry ice to TAI Diagnostics' clinical laboratory. Once the myTAI$_{HEART}$ specimen is received in TAI Diagnostics' clinical lab, the patient's cfDNA is isolated, quantified, and processed using the myTAI$_{HEART}$ test.

NOTE: Receipt of the initial recipient genotyping sample prior to ordering the myTAI$_{HEART}$ Test ensures a rapid turnaround time. More details on myTAI$_{HEART}$ specimen requirements and turnaround time can be found on our website or requested through our Customer Support Department.

SECTION X: SPECIMEN REQUIREMENTS

Use the table below to determine which number of EDTA PPT Tubes will be needed for the myTAI$_{HEART}$ test.

Table 1: Patient Weight and Blood Volume Requirements

Patient Weight	EDTA PPT Tubes	Volume of blood
0-10 kg	1 x 8.5 mL tube	8.5 mL
Greater than 10 kg	2 x 8.5 mL tubes	17.0 mL

SECTION XI: SPECIMEN COLLECTION

ITEMS NEEDED FOR COLLECTION OF THE SPECIMEN

- EDTA PPT Tubes (number of tubes determined in Table 1)
- Hospital / laboratory labels
- Parafilm
- myTAI$_{HEART}$ Test Requisition Form
- Note: If the recipient's whole blood specimen was not obtained for initial genotyping analysis at a previous pre-transplant appointment, a whole blood sample (EDTA purple top - not included in the collection kit) will need to be drawn and sent before or concurrent with submission of the first myTAI$_{HEART}$ specimen.

1. Retrieve the myTAI$_{HEART}$ testing kit from the appropriate storage location in your facility. Most often, this is your central laboratory processing department.

2. All specimen tubes must be labeled with a hospital / laboratory label containing at least two patient identifiers. It is suggested to have 5 labels available for collection and processing.

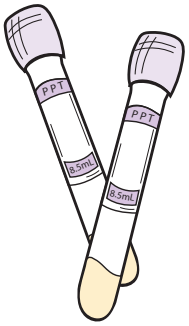
3. Using Table 1 above, determine the correct number of EDTA PPT Tubes required for the patient. Place patient labels on the chosen EDTA PPT Tubes and on each 15 ml conical centrifuge tube. According to your laboratory procedure for blood collection, draw the required volume of blood into the chosen EDTA PPT Tubes.

    a. EDTA PPT Tubes are clear blood collection tubes with a gel matrix on the bottom.

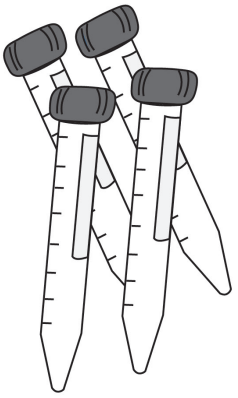
    b. 15 ml conical centrifuge tubes have screw-on lids and do not contain any additives.

4. Once the required volume of blood is collected, immediately, but gently, invert the specimen collection tube(s) end to end (180 degrees) 10 times. Do not shake or agitate the tube. Place the specimen tubes into the foam holder in an upright position.

Figure 3



EDTA PPT Tubes



15 ml Conical Centrifuge Tubes

5. Confirm the date and time of patient (recipient) specimen collection in the provided space of the myTAI$_{HEART}$ Test Requisition Form.

6. All sections of the test requisition form should be completed except for the yellow fields. Plasma spin information will be completed by the processing lab prior to send out. Refer to SECTION XIII: TEST REQUISITION FORM AND TEST ORDERS for more detailed information on filling out the test requisition form.

7. The EDTA PPT Tubes must not be sent through a pneumatic tube system. Walk the specimen and kit to your laboratory processing area. Hand off the specimen to the appropriate laboratory personnel who will immediately begin processing the whole blood sample.

SECTION XII: SPECIMEN PROCESSING - ISOLATION OF PLASMA FROM WHOLE BLOOD

NOTE: Whole blood must be processed within two hours of blood draw

1. Upon receipt in the laboratory processing area, confirm that all labels match each other as well as the information on the test requisition form.

2. Place the patient's whole blood specimen and the empty 15 ml conical centrifuge tubes into a rack on the laboratory bench.

3. On the test requisition form, fill out the plasma information section (yellow) with the following information:

Figure 4: Plasma Spin Information on the Test Requisition Form

PLASMA SPIN DATE	PLASMA SPIN TIME	INITIALS
/ /	: ☐ AM ☐ PM	

    a. PLASMA SPIN DATE: Enter the date the whole blood sample is spun in the laboratory.

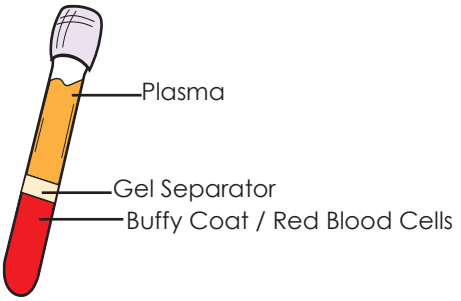
    b. PLASMA SPIN TIME: Enter the spin time as the onset of the spin.

    c. INITIALS: The date and time of the spin must be initialed by the person performing the spin.

4. Set a variable speed centrifuge to 1100 x g (RCF). Confirm that the speed is in RCF and **not** RPM.

5. SPIN 1 - Place the EDTA PPT Tube(s) into a swinging bucket rotor in the centrifuge. Spin at 1100 x g for 10 minutes. After spinning, the plasma layer will be in the top layer, followed by the gel separator. Immediately below the gel separator lies the buffy coat and red blood cells. Place the tube in a rack on the laboratory bench.

Figure 5: Separation of Plasma



6. Gather the appropriate number of 15 ml conical centrifuge tubes based on the volume of blood collected from the patient.
    a. If 8.5 mL of blood was collected from the patient, remove the blue screw cap from one of the 15 mL conical centrifuge tubes.
    b. If 17 mL of blood was collected from the patient, remove the blue screw cap from two of the 15 mL conical centrifuge tubes.
7. Remove the cap from the EDTA PPT Tube(s) containing the patient's separated blood specimen.
    a. Only work with one patient specimen at a time to prevent cross contamination of plasma.
8. Carefully decant the entire volume of separated plasma from one of the EDTA PPT Tubes into one of the 15 mL conical centrifuge tubes. If two whole blood tubes were collected from the patient, remove the cap from the second EDTA PPT Tube and decant the entire volume of plasma into the second 15 mL conical centrifuge tube. **Note: Insufficient plasma volume may result in sample failure.**
9. Tightly screw the top on to the 15 mL conical centrifuge tube(s). Place the cap back onto the EDTA PPT Tube(s).
10. Cover the top of the EDTA PPT Tube(s) (containing the remaining buffy coat and red blood cells) with parafilm and place into the provided foam rack.
11. SPIN 2 - Confirm that the centrifuge speed is set at 1100 x g (RCF not RPM) and place the conical centrifuge tube(s) which now contains the patient's plasma back into the swinging bucket rotor of the centrifuge. Centrifuge the plasma a second time at 1100 x g for 10 minutes.
12. Once spinning is complete, place the re-spun plasma into a rack on the laboratory bench.
13. Remove the cap from the remaining (unused) 15 mL conical centrifuge tube(s). Remove the cap from the conical centrifuge tube(s) which contains the re-spun plasma.
14. Take care to avoid the pellet at the bottom of the tube. Use a provided sterile transfer pipette to transfer the plasma from one of the conical centrifuge tubes and dispense it into one of the clean conical centrifuge tubes. If two tubes of plasma were spun in step 11, use the remaining, sterile transfer pipette to transfer the plasma from the second spin tube to the last clean conical centrifuge tube. **Do not combine and mix plasma from different tubes drawn from the same patient.**
15. Place the cap on the centrifuge tube(s) containing the patient's plasma (spun a total of two times). Tighten and cover with parafilm. Place in the foam rack with the EDTA PPT Tube(s).
16. Discard the conical centrifuge tubes that were used to spin the plasma in step 5 . Discard the transfer pipette.
17. You will now have the following labeled tubes in the foam rack:
    a. 15 mL conical centrifuge tube(s) with the patient's plasma (spun two times).
    b. EDTA PPT Tube(s) with the patient's buffy coat and red blood cells.
18. Confirm that each tube is labeled with at least two patient identifiers and that the information matches the test requisition form.
19. Place the foam rack containing the labeled tubes into a freezer (-20° or colder) until specimen is frozen (approximately 1 hour).

SECTION XIII: TEST REQUISITION FORM AND TEST ORDERS

All sections of the test requisition form must be completed each time the myTAI$_{HEART}$ test is ordered. The completed test requisition form must be sent with the specimen to TAI Diagnostics. It is highly recommended that a copy of the requisition form also be faxed immediately upon completion to TAI Diagnostics (1-888-300-9674) so that the receiving laboratory can begin preparation for receipt of the specimen.

1. PATIENT INFORMATION:
    a. Complete all sections of the patient information section.
    b. Enter ICD-10 / Diagnosis codes.
    c. Confirm that the patient meets the specific intended use criteria for the test. This section needs to be signed and dated by a medical provider.
2. TEST(S) REQUESTED SECTION:
    a. Select "myTAI$_{HEART}$ (Product Code: HRT1000)."
    b. If ordering Recipient Genotyping concurrently with the patient's myTAI$_{HEART}$ test, also select "Recipient Genoytping (Product Code: HRT1100)."
    c. Confirm the collection date and time.
    d. Confirm the plasma spin date, time, and processor initials are entered in the yellow section of the test requisition form.
3. PROVIDER / ORDERING PHYSICIAN INFORMATION: These sections should be filled out completely and accurately to ensure that patient reports are delivered in a timely manner.
4. REPORT DELIVERY: Select all methods in which result reports should be delivered for the patient.
5. REQUIRED DOCUMENTATION / SPECIAL INSTRUCTIONS: Be sure to include any required documentation with the test requisition form (This includes NY State Non-Permitted Laboratory Test Request approval letter, Medicare signed ABN form, and any relevant medical records).
6. BILLING: Select the desired method of billing and complete the corresponding section in its entirety.

SECTION XIV: NOTICE OF SPECIMEN REJECTION

SPECIMENS WILL BE SUBJECT TO REJECTION FOR THE FOLLOWING REASONS:

- Incomplete and unsigned test requisition.
- Improperly labeled tubes (missing patient identifiers or labels).
- Improper shipment of samples.
- Inadequate quality or quantity of specimen.

TAI Diagnostics will contact the requesting provider regarding an unacceptable specimen and will discuss the options for proceeding at that time.

SECTION XV: SPECIMEN SHIPPING

ITEMS REQUIRED FOR SHIPPING myTAI$_{HEART}$ SPECIMENS TO TAI DIAGNOSTICS

- Frozen patient (recipient) plasma specimen (in the 15 mL conical centrifuge tube) and remaining buffy coat / red blood cells (in the EDTA PPT Tubes)
- Foam rack
- Specimen biohazard bag
- Completed test requisition form
- Styrofoam shipping box with outer transport box
- Overnight return shipping label
- Dry Ice (approximately 7 pounds) and provided dry ice shipping label
- Packaging tape

IMPORTANT SAFETY NOTES REGARDING SHIPPING ON DRY ICE

- When handling dry ice, follow your laboratory's safety procedures.
- Never handle dry ice with your bare hands.
- Use dry ice in a ventilated area.
- Store dry ice in an appropriate dry ice storage bin. Do not use airtight containers as these may provide an explosive hazard.
- Dry ice is a skin and eye irritant.
- Use appropriate personal protective equipment when handling dry ice.
- Once you begin this process, work very quickly. Make sure that specimen being shipped DOES NOT THAW.

SHIPPING myTAI$_{HEART}$ SPECIMENS ON DRY ICE

1. Prepare the shipper by removing the Styrofoam container and any contents from the transport box.
2. Have dry ice ready and keep the samples in the freezer as long as possible.
3. Confirm that a hospital label with two patient identifiers is affixed to the outside of all specimen tubes, and that the caps are on tight and wrapped with Parafilm.
4. Place the tubes in the foam rack and place the rack inside of the specimen biohazard bag.
5. If ordering Recipient Genotyping concurrently with a myTAI$_{HEART}$ test, please package the patient's whole blood specimen along with the myTAI$_{HEART}$ plasma specimen on dry ice.
6. Prior to shipping, it is recommended that a copy of the test requisition form be faxed to Customer Support at 1-888-300-9674. Fold the completed test requisition form and place it into the large outer pouch of the specimen biohazard bag. Remove the adhesive liner from the flap of the biohazard bag. Press excess air out of the specimen biohazard bag, fold the flap over and seal tightly.
7. Place the biohazard bag containing the samples into the Styrofoam shipping box in an upright position prior to filling with dry ice. Use one shipping box per patient.
8. Fill the Styrofoam shipper with dry ice as full as possible. The Styrofoam lid should sit tightly on the box. Confirm that there is no gap between the lid and the box. Secure the Styrofoam lid tightly with packaging tape and place it inside of the provided cardboard shipping box.
9. Seal the cardboard shipping box with packaging tape.
10. Affix the dry ice label on an outside panel of the provided box. Confirm the dry ice shipping information is visible on the outer shipping box and indicates the appropriate weight of dry ice (7 lbs).
11. TAI Diagnostics uses UPS Next Day Air Shipping Service. FedEx labels are also provided in the kit.
    a. Affix the shipping label to the top of the myTAI$_{HEART}$ shipping box.

TAI Diagnostics accepts deliveries Monday - Friday. Contact TAI Diagnostics if needing to ship samples outside of our normal business hours. The laboratory is closed on all major holidays.

INFORMATION:

www.taidiagnostics.com
customersupport@taidiagnostics.com
PHONE: 1-888-214-3151 • FAX: 1-888-300-9674

SECTION XVI: REFERENCES

1. OPTN / SRTR Annual Report (http://www.ustransplant.org/annual_reports/current/).
2. ISHLT report 2011. J Heart Lung Transplant Oct; 30(10), 1071-1132 (2011). PMID: 21962015
3. Kaczmarek, I., et al. J Heart Lung Transplant May;26(5), 511-515 (2007). PMID: 17449422
4. Ragalie W, Stamm K, Mahnke D et al. Noninvasive Assay for Donor Fraction of Cell-Free DNA in Pediatric Heart Transplant Recipients. J Am Coll Cardiol. 2018;71(25):2982-2983. doi:10.1016/j.jacc.2018.04.026.PMID: 29929623

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